IN THE CLAIMS:

Please amend the claims as follows.

1. (Currently amended) A method of identifying a secondary drug target comprising:

(a) providing a cell having a genome, including at least one primary gene defect;

(b) effecting one or more mutations in said genome of said cell~~,at one or more secondary sites~~;

(c) selecting at least one secondary site mutation that results in a gene or protein that is non-functional and which proves lethal to said cell; and

(d) determining the ~~gene product of said lethal secondary site~~ identity of said gene or protein that is non-functional to provide a secondary drug target.

2. (Currently amended) The method of claim 1 in which said primary gene defect is found in ~~or associated with~~ a human tumor cell.

3. (Currently amended) The method of claim 1 in which said primary gene defect is analogous or homologous to a defect found in ~~or associated with~~ a human tumor cell.

4. (Original) The method of claim 1 in which said primary gene defect results in the alteration, loss, inhibition, enhancement, or gain of a function.

5. (Original) The method of claim 4 in which said function includes the suppression of tumor growth, DNA damage checkpoint, DNA mismatch repair, nucleotide excision repair, O6-methylguanine reversal, double-strand break repair, DNA helicase function, signaling, cell cycle control or apoptosis.

6. (Original) The method of claim 5 in which said signaling function includes signal transduction, tissue growth factor signaling, autocrine loop signaling, or paracrine loop signaling.

7. (Original) The method of claim 1 in which said primary gene defect includes a defect in the gene coding for pp16, p53, ATM, MSH2, MLH1, XP-A, XP-B, MGMT, BRCA2, BRCA1, BLM, RAS, NF1, MYC, PTH, Cyclin D, Cyclin E, p27kip1, or BCL-2.

Claim 8. (Canceled).

Claim 9. (Canceled).

10. (Currently amended) The method of claim 1 in which said secondary site mutation is effected within a gene selected from the group consisting of ~~cdc9, cdc2,~~ a gene encoding a gene product exhibiting polymerase δ exonuclease function, a gene encoding a gene product exhibiting polymerase ε exonuclease function, a gene encoding a ribonucleotide reductase, ~~mec1,~~ a rad53 - like gene, ~~cdc53, cdc34, cdc14, cdc15,~~ a gene encoding NUP170, ~~dbf2,~~ a gene encoding CLN2, ~~rad3, rad9, rad27, cdc8,~~ a gene encoding Mlu-1 box binding factor, ~~slm1,~~ a gene encoding MBF, a gene encoding PCNA, ~~or~~ and a gene encoding a replication fork protein.

11. (Currently amended) The method of claim 1 in which said secondary site mutation is effected within a gene coding for a gene product selected from PIK-related kinase ~~(mec1)~~, E2 ubiquitin carrier protein ~~(cdc34)~~, E3 ubiquin ligase ~~(cdc53)~~, ubiquitin ligase ~~(skp1)~~, protein phosphatase ~~(cdc14)~~ and nuclear pore protein ~~(NUP170)~~.

12. (Original) The method of claim 1 in which said secondary site mutation is effected within a gene having a mammalian analog or homolog.

13. (Original) The method of claim 12 in which said mammalian homolog is selected from the group consisting of a gene encoding a DNA ligase I, a gene encoding a DNA polymerase, a gene encoding a ribonucleotide reductase, a gene encoding a FEN-1, a gene encoding Cyclin D, a gene encoding Cyclin E, an AT-related gene, a gene encoding NUP-155 or a gene encoding an isozyme.

Claim 14. (Canceled).

15. (Original claim) The method of claim 1 which further comprises using said secondary drug target to screen for a drug or drug candidate.

16. (Original claim) The method of claim 15 in which said drug or drug candidate interacts with, binds to, or inhibits a gene product selected from the group consisting of DNA ligase, DNA polymerase, polymerase δ exonuclease, polymerase ε exonuclease, ribonucleotide reductase, a subunit of transcriptional activator, a transcription factor, PCNA, a replication fork protein, PIK-related kinase, recombinase, E3 ubiquitin ligase, E2 ubiquitin carrier protein, a protein tyrosine phosphatase, a nuclear pore protein, cyclin, DNA repair exonuclease, thymidylate kinase, a gene product of slm 1, ribonucleottide reductase, or a transcriptional activator.

17. (Original claim) The method of claim 15 in which said drug or drug candidate inhibits the growth of a human tumor.

18. (Currently amended) A method of rational antitumor drug design comprising: (i) providing a genetically tractable organism harboring an altered gene that is analogous or homologous to a primary tumor defect, (ii) performing a synthetic lethal screen to identify a secondary target gene, (iii) determining an analogous or homologous secondary target in

mammalian cells, and (iv) using said analogous or homologous secondary target to screen for a drug or drug candidate having antitumor activity, wherein said genetically tractable organism is selected from the group consisting of *Saccharamyces cerevisiae*, *Schizzosaccaromyces pombe*, *Caenorhabditis elegans*, and *Drosophila melanogaster*.

19. (Original claim) The method of claim 18 in which the drug or drug candidate comprises a small molecule.

20. (Original claim) The method of claim 17 which further comprises validating the synthetic lethality of said analogous or homologous secondary target in a mammalian cell relative to a mammalian non-tumor cell.

21. (Withdrawn) A method of treating a cancer comprising administering to a cancer patient an effective amount of an anticancer agent, which anticancer agent interacts with, binds to, or inhibits a gene product of a secondary target gene present in a mammalian tumor cell.

22. (Withdrawn). The method of claim 21 in which said target gene is identified by performing a synthetic lethal screen.

23. (Original) The method of claim 1 in which said primary gene defect includes a defect in a gene coding for PIK-related kinase (mec1).

24. (Original) The method of claim 1 in which said secondary site mutation is effected with a gene selected from the group consisting of RNR1, RNR4, CDC8, CDC21, SHM2, PRII, CDC17, MBP1, SLM1, SLM2, SLM3, and SLM4.

25. (Original) The method of claim 1 in which said primary gene defect includes a defect in a gene coding for PIK-related kinase (mec1), and ssaid secondary site mutation is effected with a gene selected from the group consisting of of RNR1, RNR4, CDC8, CDC21, SHM2, PRII, CDC17, MBP1, SLM1, SLM2, SLM3, and SLM4.

26. (Withdrawn) A pharmaceutical composition comprising an effective amount of an agent derived from the gene product of a lethal secondary site mutation, the expression of which proves lethal to a cell having at least one primary gene defect, and a pharmaceutically acceptable carrier or diluent, said agent comprising said gene product, active fragments thereof, derivatives or analogs thereof, or small molecule or peptide mimetics thereof.

27. (Withdrawn) The pharmaceutical composition of claim 26, wherein the lethal secondary site mutation is a mutation within a yeast gene selected from the group consisting of cdc9, cdc2, a gene encoding a gene product exhibiting polymerase exonuclease function, a gene encoding a gene product exhibiting polymerase E exonuclease function, a gene encoding a ribonucleotide reductase, mecI, rad53 like gene, cdc53, cdc34, cdcI4, 15 cdcI5, a gene encoding NUPI70, dbf2, a gene encoding CLN2, rad3, rad9, rad27, cdc8, a gene encoding Mlul-box binding factor, slmI, a gene encoding MBF, a gene encoding PCNA, a gene encoding replication fork protein, RNRI, RNR2, RNR4, CDC2I, SHM2, PRII, CDCI7, MBPI, SLMI, SLM2, SLM3, and SLM4, or a human gene analogous or homologous to said yeast gene.

28. (Withdrawn) The pharmaceutical composition of claim 27, wherein the human gene comprises a gene encoding a DNA ligase I, a gene encoding a DNA polymerase, a gene encoding a ribonucleotide reductase, a gene encoding a FEN-I, a gene encoding Cyclin D, a gene encoding Cyclin E, a gene encoding NUPI55, or a gene encoding an isozyme.

29. (Withdrawn) The pharmaceutical composition of claim 27, wherein the human gene comprises an AT-related gene.

30. (Withdrawn) A pharmaceutical composition comprising an effective amount of an agent and a pharmaceutically acceptable carrier or diluent, said agent capable of inhibiting either the expression of a synthetic lethal gene or the activity of the gene product of a synthetic lethal gene that is found in a cell having at least one primary gene defect.

31. (Withdrawn) The pharmaceutical composition of claim 30 in which said agent is effective to arrest division, growth, or viability of said cell.

32. (Withdrawn) The pharmaceutical composition of claim 31 in which said agent does not arrest division, growth, or viability of a cell that does not contain said at least one primary gene defect.

33. (Withdrawn) The pharmaceutical composition of claim 30 in which said synthetic lethal gene comprises a yeast gene selected from the group consisting of cdc9, cdc2, a gene encoding a gene product exhibiting polymerase 0 exonuclease function, a gene encoding a gene product exhibiting polymerase E exonuclease function, a gene encoding a ribonucleotide reductase, mecl, rad53 like gene, cdc53, cdc34, cdcl4, cdcl5, a gene 15 encoding NUP170, dbf2, a gene encoding CLN2, rad3, rad9, rad27, cdc8, a gene encoding Mlul-box binding factor, slml, a gene encoding MBF, a gene encoding PCNA, a gene encoding replication fork protein. RNRl, RNR2, RNR4, CDC21, SHM2, -PRII, CDCI7, MBPl, SLMl, SLM2, SLM3, and SLM4, or a human gene analogous or homologous to said yeast gene.

34. (Withdrawn) The pharmaceutical composition of claim 33, wherein the human gene comprises a gene encoding a DNA ligase I, a gene encoding a DNA polymerase, a gene encoding a ribonucleotide reductase, a gene encoding a FEN-I, a gene encoding Cyclin

D, a gene encoding Cyclin E, a gene encoding NUP155, or a gene encoding an isozyme.

35. (Withdrawn) The pharmaceutical composition of claim 33, wherein the human gene comprises an AT -related gene.

36. (Withdrawn) The pharmaceutical composition of claim 30 in which said agent inhibits the activity of A TR.

37. (Withdrawn) The pharmaceutical composition of Claim 30, wherein said at least one primary gene defect results in an abnormal accumulation of a human G I/S Cyclin.

38. (Withdrawn) The pharmaceutical composition of claim 37, wherein said abnonnal accumulation of a human G lIS Cyclin is due to overexpression of or decrease in the degradation of the G lIS Cyclin.

39. (Withdrawn) The pharmaceutical composition of claim 37, wherein said human GI/S Cyclin comprises Cyclin D 1 or Cyclin E.

40. (Withdrawn) The pharmaceutical composition of claim 30, wherein said gene product is selected from (or wherein said synthetic lethal gene codes for) a human isozyme of

cdc34, a human isozyme ofcdc53, a human isozyme ofSkpl, a human isozyme ofcdcl4 andNUP155.

41. (Withdrawn) The pharmaceutical composition of claim 30, wherein said gene product is A TR or wherein said synthetic lethal gene codes for A TR.

42. (Withdrawn) A pharmaceutical composition comprising a drug in a pharmaceutically accepatable carrier or diluent, said drug selectively interacts with the expression or biological activity of at least one gene product in a cell population, said cell population I contains at least one primary gene defect, wherein exposure of said cell population to said drug arrests or reduce cell division selectively in said cell population.

43. (Withdrawn) The pharmaceutical composition of claim 42 wherein said interaction comprises total arrest, increase or reduction.

44. (Withdrawn). A method of treating cancer cells having abnormal accumulation of a human G1/S Cyclin which comprises administering a pharmaceutical composition comprising an effective amount of an agent and a pharmaceutically acceptable carrier or diluent, said agent capable of inhibiting either the expression of a synthetic lethal gene or the activity of the gene product of a synthetic lethal gene that is found in a cell having at least one primary gene defect, wherein said gene product is selected from (or wherein said synthetic lethal gene codes for) a human isozyme of cdc34, a human isozyme of cdc53, a human isozyme of skpl, a human isozyme of cdcl4 and NUP155.

45. (Withdrawn) The method of claim 44 wherein said gene product is an ATR or wherein said synthetic lethal gene codes for A TR.

46 (Withdrawn) The method of claim 45 wherein said ATR is an ATR-dk.